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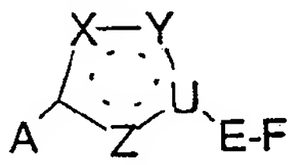

(I)

(57) Abstract

The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the specification, in the manufacture of a medicament for use in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

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5-HT4 RECEPTOR ANTAGONISTS

This invention relates to the use of compounds as 5-HT_4 receptor antagonists in the treatment of gastrointestinal disorders, CNS disorders and/or cardiovascular disorders, and to certain novel compounds having 5-HT_4 receptor antagonist activity.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that ICS 205-930, which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor.

PCT/GB91/00650 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

Some 5-HT_3 receptor antagonists have been disclosed as of potential use in the treatment of certain aspects of irritable bowel syndrome [see EP-A-189002 (Sandoz Limited) and EP-A-200444 (Beecham Group p.l.c)].

5-HT_3 receptor interactions which are of potential use in the treatment of IBS are those associated either with the visceral pain and abnormal perception of sensation aspects of this disease, or they are related to the ability of some 5-HT_3 receptor antagonists to cause constipation in volunteers.

Some 5-HT_3 receptor antagonists have been disclosed as of potential use in the treatment of gastrointestinal disorders associated with upper gut motility [see EP-A-226266 (Glaxo Group Ltd.) and EP-A-189002 (Sandoz Limited)]. 5-HT_3 receptor antagonists are also well known antiemetics, such as ondansetron, granisetron and tropisetron (see Drugs of the Future 1989, 14 (9) p.875 - F.D. King and G.J. Sanger).

EP-A-328200 and U.S. Patent 4952587 (Merck Sharp & Dohme Ltd.) disclose a group of heterocyclic compounds which are described as useful in the treatment of psychotic disorders (e.g. schizophrenia and mania);

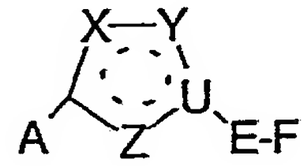
anxiety; alcohol or drug withdrawal; pain; gastric stasis; gastric dysfunction (such as occurs with dyspepsia, peptic ulcer, reflux oesophagitis and flatulence); migraine; nausea and vomiting and presenile and senile dementia (also known as Alzheimer's disease and senile dementia of the Alzheimer type respectively). Certain of the compounds are described as acting on 5-HT_3 receptors and this is attributed in whole or in part, for the pharmacological activity of these compounds. J. Med. Chem. 1991, 34, 140-51 (Swain et. al.) describes these and other compounds and their properties as 5-HT_3 receptor antagonists. J. Med. Chem. 1990, 33, 2715 describes a related group of 5-HT_3 receptor antagonists.

It has now been discovered that certain of the compounds embraced by the general formulae disclosed therein, and related compounds, have 5-HT_4 receptor antagonist properties, and are therefore of potential use in the treatment of IBS or atrial arrhythmias and stroke.

The compounds of the present invention also have a potential use in the treatment of CNS disorders such as anxiety and/or migraine, in the treatment of upper gut motility disorders and as antiemetics.

When used herein 'treatment' includes prophylaxis as appropriate.

The invention therefore provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:

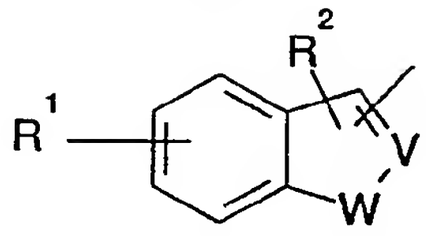


(I)

wherein

the dotted circle represents one or two double bonds in any position in the 5-membered ring; X, Y and Z independently represent oxygen, sulphur, nitrogen or carbon, provided that at least one of X, Y and Z represents oxygen, sulphur or nitrogen; U represents nitrogen or carbon;

A represents a group of formula (II):



(II)

in which:

R^1 represents hydrogen, hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, hydroxy (C_{1-6})alkyl, halogen, amino, cyano, $-CONR^6R^7$ or $-SO_2NR^6R^7$, in which R^6 and R^7 independently represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

R^2 represents hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylcarbonyl;

V represents nitrogen,

-CH or -C-

and

W represents oxygen, sulphur or

$-NR^8$

in which

R^8 represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

E represents a straight or branched alkylene or alkenylene chain containing from 1 to 5 carbon atoms and optionally containing an -O-, -S-, -NH- or -Nalkyl- linkage; and

F represents:

a) a non-aromatic azacyclic ring system or a non-aromatic azabicyclic ring system having carbon bridgehead(s); or.

b) a group of formula $-NR^aR^b$ wherein one of R^a and R^b is hydrogen or C_{1-6} alkyl and the other is hydrogen, C_{1-10} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or aryl(C_{1-6})alkyl;

in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

In the above formula (II):

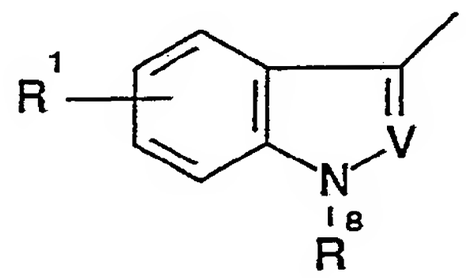
V preferably represents N or CH;

W preferably represents NR^8;

R^1 preferably represents H; and

R^2 preferably represents -CH-.

The group A in formula (I) is therefore preferably as indole or indazole of formula (IIA):



(IIA)

wherein V is N, CH or CHR^2 and R^1 are as defined for formula (I) above, and are preferably as described for formula (II) above.

The group A in formula (I) may also be replaced by a substituted phenyl moiety, as described in formula (III) of EP-A-189002, for example as described in Example 2 hereinafter.

Suitable examples of A, X, Y, Z, E and F are as described in EP-A-328200, or as in the following Examples.

Examples of alkyl or alkyl containing groups include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} or C_{12} branched, straight chained or cyclic alkyl, as appropriate. C_{1-4} alkyl groups include methyl, ethyl *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Cyclic alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Alkenyl includes all suitable values including *E* and *Z* forms.

Aryl includes phenyl and naphthyl.

Halo includes fluoro, chloro, bromo and iodo.

Suitable examples of F are as described in EP-A-328200, i.e. those having an R^5 substituent wherein the group E is optionally attached through R^5. Other examples of F of interest are those described for the compounds of the Examples hereinafter.

Suitable examples of compounds of formula (I) include that described in Example 21 of EP-A-328200, 1-methyl-3-[5-(2-(1-piperidyl)ethyl)-1,2,4-oxadiazol-3-yl]indole. Other suitable examples of compounds of formula (I) are described in the Examples hereinafter.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

Some of the compounds of formula (I) have at least one asymmetric centre and exist as more than one stereoisomeric form. The invention extends to each of these forms and to mixtures thereof including racemates.

The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-HT_4 receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

It is believed that platelet-derived 5-HT induces atrial arrhythmias which encourage atrial fibrillation and atrial disorders are associated with symptomatic cerebral and sytemic embolism. Cerebral embolism is the most common cause of ischaemic stroke and the heart the most common source of embolic material. Of particular concern is the frequency of embolism associated with atrial fibrillation.

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol Pharmacol., 34, 880-887). Activity may be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional

stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT_4 receptors, and hence that administration of a 5-HT_4 antagonist is of potential benefit in relieving a migraine attack.

5-HT_4 receptor antagonist activity may be identified according to standard methods, such as those described hereinafter.

Examples of 5-HT_4 receptor antagonists include ICS 205-930 (tropisetron), which is described in the above mentioned patent references, R 50 595 (Janssen), which is described in FR76530 and Eur.J. Pharmacol., *181* 119-125 (1990), and SDZ 205-557, which is described by K.H. Buchheit and R. Gamse in Naunyn-Schmiedeberg's Arch. Pharmacol., **343** (Suppl.), R101 (1991).

In one aspect, the compound of formula (I) is a more potent antagonist at 5-HT_4 receptors than at 5-HT_3 receptors.

Preferably, the 5-HT_4 receptor antagonist of formula (I) is in substantially pure pharmaceutically acceptable form.

The compounds of formula (I) may be prepared as described in EP-A-328200 and US 4952587, and in the Examples and Descriptions hereinafter.

The administration of the compound may be by enteral such as oral, rectal or nasal, sublingual, transdermal or parenteral administration.

An amount effective to treat the disorder hereinbefore described depends on the usual factors such as the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 50 mg for example 0.5 to 10 mg, of the active ingredient. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a

day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 50 mg, for example 0.1 to 5 mg, that is in the range of approximately 0.001 to 1 mg/kg/day, more usually 0.005 to 0.2 mg/kg/day.

For oral or parenteral administration, it is greatly preferred that the compound is administered in the form of a unit-dose composition, such as a unit dose oral or parenteral composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl

cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the 5-HT_4 receptor antagonist and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the treatment concerned.

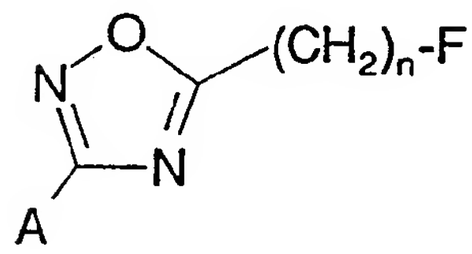
The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment and/or prophylaxis of irritable bowel syndrome, gastro-oesphageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine. Such treatment and/or prophylaxis may be carried out as hereinbefore described.

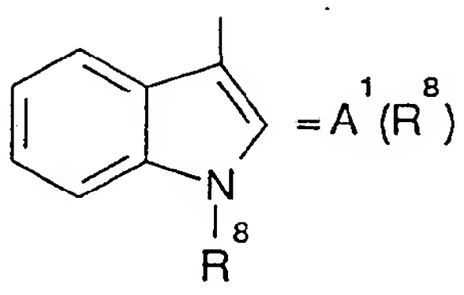
The present invention also provides a method of treatment and/or prophylaxis of irritable bowel syndrome, gastro-oesphageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

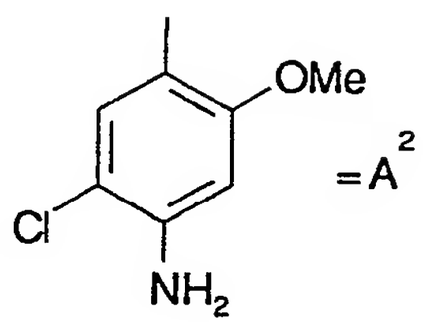
The present invention further provides a pharmaceutical composition for use in the treatment and/or prophylaxis of irritable bowel syndrome , gastro-oesphageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. Such compositions may be prepared in the manner as hereinbefore described.

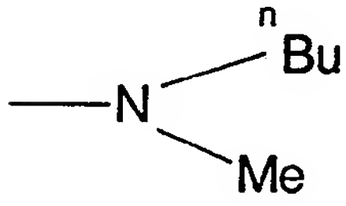
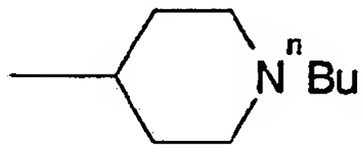
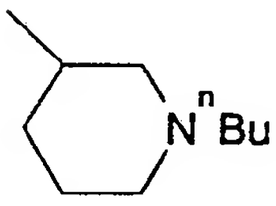
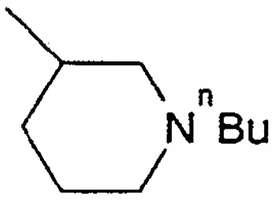
The following Examples illustrate compounds for use in the invention, the following Descriptions illustrate the preparation of intermediates.

Examples 1 to 29

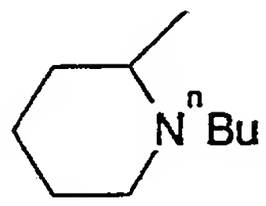
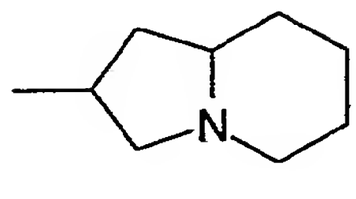
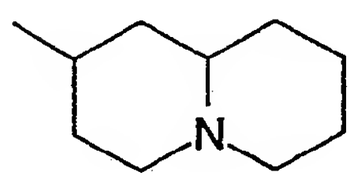
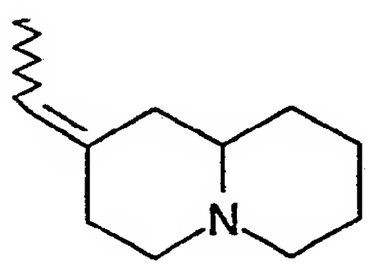
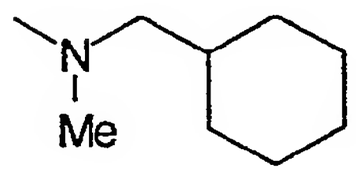
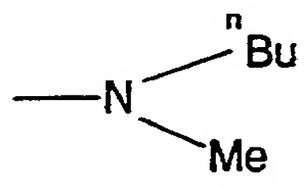
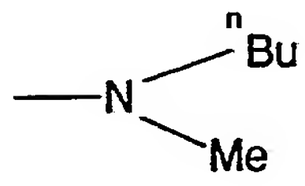
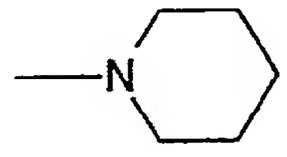
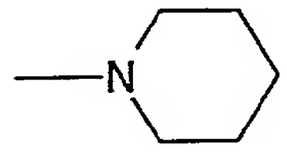




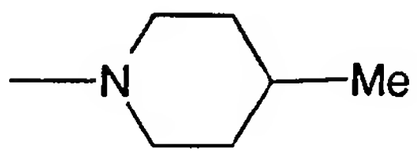
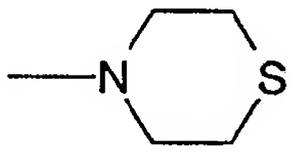
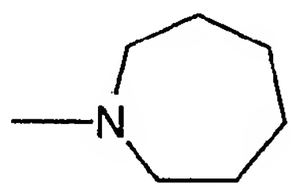
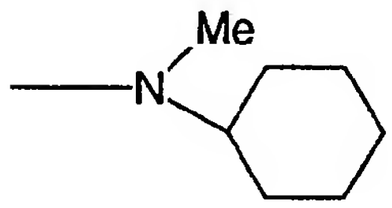
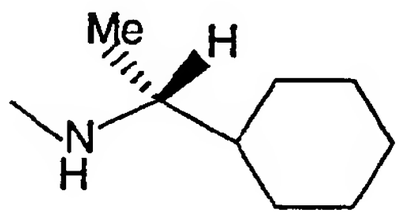
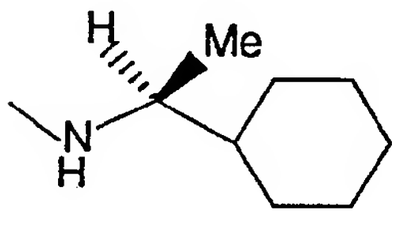
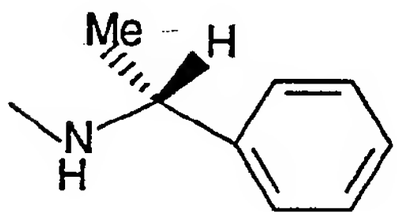
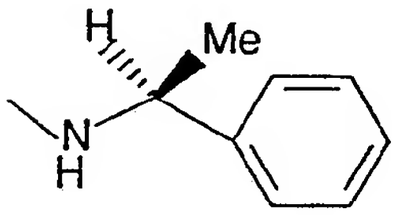


Example	A	n	F
E1	A^1	3	
E2	A^1(Me)	0	
E3	A^1(Me)	1	
E4	A^1(Me)	0	
E5	A^1(Me)	1	

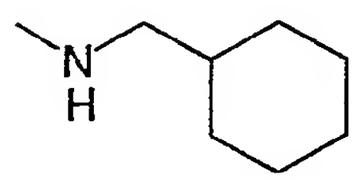
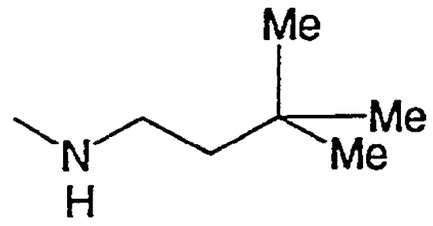
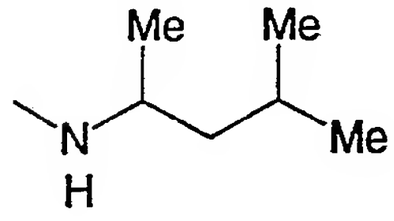
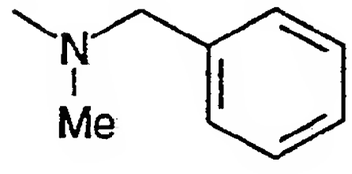
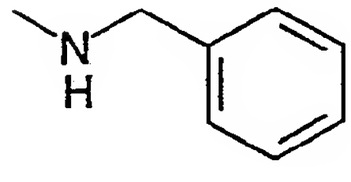
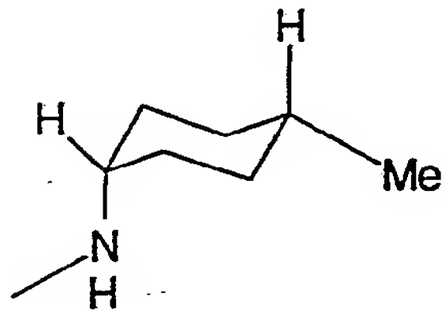
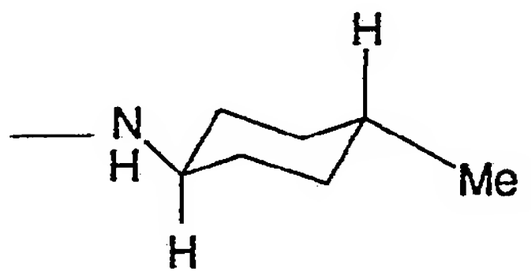
Examples 1 to 29 (cont'd)

Example	**A**	**n**	**F**
E6	A^1(Me)	1	
E7	A^1(Me)	1	
E8	A^1(Me)	1	
E9	A^1(Me)	0	
E10	A^1(Me)	1	
E11	A^1(Me)	1	
E12	A^1(Me)	4	
E13	A^1(Et)	3	
E14	A^2	3	

Examples 1 to 29 (cont'd)

Example	A	n	F
E15	A^1(Me)	2	
E16	A^1(Me)	2	
E17	A^1(Me)	2	
E18	A^1(Me)	2	
E19	A^1(Me)	2	 (R)
E20	A^1(Me)	2	 (S)
E21	A^1(Me)	2	 (R)
E22	A^1(Me)	2	 (S)

Examples 1 to 29 (cont'd)

Example	A	n	F
E23	A^1(Me)	2	
E24	A^1(Me)	2	
E25	A^1(Me)	2	
E26	A^1(Me)	2	
E27	A^1(Me)	2	
E28	A^1(Me)	2	 (cis)
E29	A^1(Me)	2	 (trans)

Example 1

5-[3-(N-Methylbutylamino)propyl]-3-[1-methyl-1H-indol-3-yl]-1,2,4-oxadiazole (E1)

1-Methyl-1H-indole-3-carboxamide oxime (C.J. Swain *et al*, J.Med. Chem, 1991, **34**, 147) (0.250g, 1.33 mmol) was dissolved in dry THF (8 ml) with stirring and treated with ground 4A^0 molecular sieves (1g), under nitrogen. After 30 minutes sodium hydride (80% dispersion in mineral oil) (0.044g, 1.46 mmol) was added. The mixture was then heated to reflux, after 30 minutes, the mixture was allowed to cool momentarily, and a solution of ethyl-4-*N*-methylbutylaminobutyrate (0.293g, 1.46 mmol) in dry THF (2 ml) was added. The mixture was then heated to reflux. After 6h, the reaction mixture was allowed to cool, and was then filtered. The filter pad was then washed with THF (2x) and the filtrate evaporated under reduced pressure. The residue was then purified by silica-gel chromatography, eluting with ethyl acetate/methanol 20:1 to afford the title compound as a colourless oil (0.243g, 56%), which was converted to its hydrochloride salt, m.pt, 174-175^{o}C.

^{1}H NMR (250 MHz, CD_3SOCD_3)

δ: 10.8 (s, 1H), 8.12 (s, 1H), 8.03 (d, J=8Hz, 1H), 7.58 (d, J=8Hz, 1H), 7.20-7.37 (m, 2H), 3.90 (s, 3H), 2.96-3.32 (m, 6H), 2.77 (s, 3H), 2.17-2.35 (m, 2H), 1.61-1.78 (m, 2H), 1.28-1.41 (m, 2H), 0.92 (t, J=6Hz, 3H).

Examples 2 to 12

The following compounds were prepared analogously:

5-[N-Butyl-4-piperidyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E2)

mp 69-70^{o}C

^{1}H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.24 (dd, J=8 and 1Hz, 1H), 7.80 (s, 1H), 7.22-7.42 (m, 3H), 3.89 (s, 3H),

2.93-3.10 (m, 3H), 2.38 (t, J=8Hz, 2H), 2.00-2.23 (m, 6H), 1.45-1.60 (m, 2H), 1.22-1.41 (m, 2H), 0.92 (t, J=6Hz, 3H).

5[N-Butyl-4-piperidylmethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E3)

mp 182-183°C (HCl salt)

^1H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.22 (dd, J=8 and 1Hz, 1H), 7.80 (s, 1H), 7.24-7.42 (m, 3H), 3.89 (s, 3H), 2.95 (m, 2H), 2.89 (d, J=8Hz, 2H) 2.32 (t, J=8Hz, 2H), 1.73-2.02 (m, 5H), 1.42-1.58 (m, 2H), 1.21-1.42 (m, 2H), 0.92 (t, J=6Hz, 3H).

5-[N-Butyl-3-piperidyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E4)

mp 219-220°C (HCl salt)

^1H NMR (270 MHz, $CDCl_3$) (HCl salt)

δ: 12.80-12.98 br (s, 1H), 8.20 (dd, J=8 and 1Hz, 1H), 7.79 (s, 1H), 7.24-7.42 (m, 3H), 4.21 (m, 1H), 3.97 (m, 1H), 3.89 (s, 3H), 3.62 (m, 1H), 2.92-3.08 (m, 2H), 2.48-2.79 (m, 3H), 1.32-1.52 (m, 2H), 1.00 (t, J=6Hz, 3H).

5-[N-Butyl-3-piperidylmethyl]-3-(1-methylindol-3-yl]-1,2,4-oxadiazole (E5)

mp 195-198°C (HCl salt)

^1H NMR (250 MHz, CD_3SOCD_3)

δ: 10.80 br (s, 1H), 8.15 (s, 1H), 8.02 (d, J=8Hz, 1H), 7.58 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 3.90 (s, 3H), 3.55 (m, 1H), 2.92-3.10 (m, 4H), 2.68-2.85 (m, 2H), 1.61-1.92 (m, 6H), 1.13-1.40 (m, 4H), 0.90 (t, J=6Hz, 3H).

5-[N-Butyl-2-piperidylmethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E6)

mp 65-68°C (oxalate salt)

^{1}H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.21 (dd, J=8 and 1Hz, 1H), 7.80 (s, 1H), 7.24-7.40 (m, 3H), 3.89 (s, 3H), 3.00-3.30 (m, 2H), 2.40-2.80 (m, 2H), 1.40-1.80 (m, 9H), 1.22-1.38 (m, 2H), 0.92 (t, J=6Hz, 3H).

5-[Indolizidin-2-ylmethyl]-3(1-methylindol-3-yl)-1,2,4-oxadiazole (E7)

Higher RF isomer

mp 215-216°C (HCl salt)

^{1}H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.22 (dd, J=8 and 1Hz, 1H), 7.79 (s, 1H), 7.24-7.42 (m, 3H), 3.89 (s, 3H), 3.05 (m, 3H), 2.93 (dd, J=10 and 1Hz, 1H), 2.52 (m, 1H), 2.40 (t, J=8Hz, 1H), 2.18 (m, 1H), 1.71-2.03 (m, 5H), 1.52-1.70 (m, 1H), 1.17-1.32 (m, 3H).

Lower RF isomer

mp 215-218°C (HCl salt) (free base)

^{1}H NMR (250 MHz, $CDCl_3$)

δ: 8.22 (dd, J=8 and 1Hz, 1H), 7.79 (s, 1H), 7.20-7.40 (m, 3H), 3.89 (s, 3H), 3.38 (t, J=8Hz, 1H), 3.08 (m, 1H), 2.94 (m, 2H), 2.80 (m, 1H), 1.50-2.05 (m, 9H), 1.18-1.41 (m, 2H).

5-(Quinolizidin-2-ylmethyl)-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E8)

mp 173-175°C (HCl salt)

^{1}H NMR (250 MHz, CD_3SOCD_3) (HCl salt)

δ: 10.4 (s, 1H), 8.14 (s, 1H), 8.03 (d, J=8Hz, 1H), 7.58 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 3.89 (s, 3H), 3.30 (m, 1H), 2.80-3.15 (m, 5H), 2.20 (br s, 1H), 1.40-2.00 (m, 10H).

5-(Quinolizidin-2-ylmethylene)-3-(methylindol-3-yl)-1,2,4-oxadiazole (E9)

Higher RF isomer

mp 226-227°C (HCl salt)

^{1}H NMR (250 MHz, CD_3SOCD_3) (HCl salt)

δ: 11.20 (br, s, 1H), 8.18 (s, 1H), 8.05 (d, J=8Hz, 1H), 7.60 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 6.60 (s, 1H), 4.05 (d, J=11Hz, 1H), 3.89 (s, 3H), 3.55 (m, 1H), 2.70-3.25 (m, 6H), 1.60-2.00 (m, 6H), 1.40-1.60 (m, 1H).

Lower RF isomer

mp 227-228°C (HCl salt)

^{1}H NMR (250 MHz, CD_3SOCD_3) (HCl salt)

δ: 11.15 (br, s, 1H), 8.20 (s, 1H), 8.06 (d, J=8Hz, 1H), 7.60 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 6.61 (s, 1H), 4.08 (d, J=10Hz, 1H), 3.89 (s, 3H), 3.58 (m, 1H), 3.40 (m, 1H), 2.54-3.30 (m, 6H), 1.80-2.10 (m, 5H), 1.40-1.60 (m, 1H).

5[2-(N-Methylcyclohexylmethylamino)ethyl]-3(1-methylindol-3-yl)-1,2,4-oxadiazole (E10)

mp 162-163°C (HCl salt)

^{1}H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.27 (dd, J=8 and 1Hz, 1H), 7.85 (s, 1H), 7.30-7.47 (m, 3H), 3.98 (s, 2H), 3.89 (s, 3H), 2.44 (s, 3H), 2.33 (d, J=8Hz, 2H), 1.50-1.90 (m, 5H), 1.10-1.40 (m, 4H), 0.82-1.00 (m, 2H).

5-(N-Methylbutylaminomethyl)-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E11)

mp 182-183°C (HCl salt)

^{1}H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.24 (dd, J=8 and 1Hz, 1H), 7.82 (s, 1H), 7.29-7.42 (m, 3H), 3.95 (s, 2H), 3.89 (s, 3H), 2.55 (t, J=6Hz, 2H) 2.42 (s, 3H), 1.50-1.62 (m, 2H), 1.25-1.47 (m, 2H), 0.94 (t, J=6Hz, 3H).

5-[4-(N-Methylbutylamino)butyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E12)

mp 130-132°C (HCl salt)

^{1}H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.22 (dd, J=8 and 1Hz, 1H), 7.79 (s, 1H), 7.25-7.41 (m, 3H), 3.88 (s, 3H), 2.98 (t, J=6Hz, 2H), 2.30-2.44 (m, 4H), 2.20 (s, 3H), 1.90 (m, 2H), 1.21-1.70 (m, 6H), 0.92 (t, J=6Hz, 3H).

Example 13

5-[(3-(Piperidino)propyl)]-3-(1-ethyl-1H-indol-3-yl)-1,2,4-oxadiazole (E13)

1-Ethylindole-3-ylcarboxamide oxime (200 mg, 0.98 mmol, prepared by the general method of EP-A-328200) was dissolved in anhydrous THF (4 ml) containing 4-A° powdered molecular sieves (300 mg). The mixture was

stirred for 30 mins., sodium hydride (80% dispersion in oil) (40 mg, 1.3 mmol) was added and the mixture was heated at 60°C for 20 min. It was then cooled to RT and a solution of methyl-4-piperidinyl butyrate (364 mg, 1.98 mmol) in THF (2 mol) was added. The resulting mixture was heated at reflux for 1 hr., cooled, filtered and the filtrate concentrated under vacuum. The residue was purified by column chromatography to give the product (210 mg).

mp 190-91°C (oxalate salt).

Example 14

5-[3-(Piperidino)propyl]-3-(2-methoxy-4-amino-5-chlorophen-1-yl)-1,2,4-oxadiazole (E14)

2-Methoxy-4-amino-5-chlorobenzamide-oxime (D1) (0.250g, 1.16 mmol) was dissolved in dry THF (8 ml) and treated with ground 4A° molecular sieves (1g). The mixture was then stirred at room temperature for ½h, before NaH (80% disp. in mineral oil) (0.035g, 1.16 mmol) was added. The mixture was then heated to reflux. After ½h the reaction mixture was allowed to cool momentarily, and methyl-4-piperidinyl-butyrate (0.242g, 1.22 mmol) in dry THF (3 ml) was added. Reflux was then maintained for a further 4h. The reaction mixture was then allowed to cool, and was filtered. The filter pad was washed with THF (2x), and the filtrate was evaporated under reduced pressure to give a yellow solid. The solid was purified by silica-gel chromatography using EtOAc : MeOH 98/2 - 95/5 as eluant to give the title compound as a white solid (0.270g, 66%). m.pt 112-114°C (from CH_2Cl_2/Petrol)

^1H NMR (270 MHz, $CDCl_3$) (free base)

δ: 7.93 (s, 1H), 6.40 (s, 1H), 4.37 (s, 2H), 3.90 (s, 3H), 2.93 (t, J=6Hz, 2H), 2.30-2.48 (m, 6H), 1.98-2.12 (m, 2H), 1.50-1.62 (m, 4H), 1.35-1.49 (m, 2H).

Example 15

5-[(4-Methyl-piperidino)ethyl]-3-(1-methyl-1-H-indol-3-yl)-1,2,4-oxadiazole (E15)

5-Ethenyl-3-(1-methyl-1-H-indol-3-yl)-1,2,4-oxadiazole (D2) (0.0254 g, 1.13 mmol) was dissolved in methanol (5 ml) and 4-methyl piperidine (0.167 ml, 1.69 mmol) was added. The mixture was left standing at room temperature for 16 hours, before being evaporated under reduced pressure to give a colourless oil, which was purified by silica-gel chromatography, eluting with ethyl acetate to afford the title compound as a colourless oil that crystallised on standing. The material was then converted to its hydrochloride salt, mp 192-192°C.

^{1}H NMR (250MHz, CD_3SOCD_3) (HCl salt)

δ: 10.9 br (s, 1h), 8.13 (s, 1H), 8.03 (d, J=8Hz, 1H), 7.58 (d, J=8Hz, 1H), 7.21-7.38 (m, 2H), 3.89 (s, 3H), 3.48-3.70 (m, 6H), 2.90-3.10 (m, 2H), 1.72-1.90 (m, 2H), 1.43-1.70 (m, 3H), 0.90 (d, J=6Hz, 3H).

Examples 16 to 29

The following compounds were prepared analogously:

5-[2-(Thiomorpholino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E16)

mp 121-122°C (free base)

^{1}H NMR (250MHz, $CDCl_3$) (free base)

δ: 8.22 (dd, J=8 and 1Hz, 1H), 7.80 (s, 1H), 7.27-7.42 (m, 3H), 3.89 (s, 3H), 3.13 (m, 2H), 3.00 (m, 2H), 2.85 (m, 2H), 2,69 (m, 2H).

5-[2-(Hexamethyleneimino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E17)

mp 173-175°C (HCl salt)

^{1}H NMR (250MHz, CD_3SOCD_3) (HCl salt)

δ: 11.04 br (s, 1H), 8.12 (s, 1H), 8.03 (d, J=8Hz, 1H), 7.58 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 3.89 (s, 3H), 3.60 (s, 4H), 3.45 (m, 2H), 3.22 (m, 2H), 1.76-1.92 (m, 4H), 1.50-1.75 (m, 4H).

5[2-(N-Methylcyclohexylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E18)

mp 162-163°C (HCl salt)

^{1}H NMR (250MHz, CD_3SOCD_3) (HCl salt)

δ: 10.95 br (s, 1H), 8.22 (s, 1H), 8.04 (d, J=8Hz, 1H), 7.59 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 3.79 (s, 3H), 3.40-3.80 (m, 4H), 3.22-3.40 (m, 1H), 2.80 (d, J=6Hz, 3H), 2.10 (m, 2H), 1.82 (m, 2H), 1.08 (m, 6H).

5[2-((R)-(-)-1-Cyclohexylethylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E19)

mp 206-207°C (HCl salt)

^{1}H NMR (250MHz, CD_3SOCD_3) (HCl salt)

δ: 9.30 br (s, 1H), 8.88 br (s, 1H), 8.12 (s, 1H), 8.05 (d, J=8Hz, 1H), 7.60 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 3.89 (s, 3H), 3.40-3.58 (m, 4H), 3.10-3.25 (m, 1H), 1.60-1.88 (m, 6H), 0.98-1.38 (m, 8H).

5[2-((S)-(+)-1-Cyclohexylethylamino)ethyl]-3(1-methylindol-3-yl)-1,2,4-oxadiazole (E20)

mp 205-206°C

^{1}H NMR - as given for E19

5[2-((R)-(+)-α-Methylbenzylamino)ethyl]-3-(1-methylindol-3-yl]-1,2,4-oxadiazole (E21)

mp 128-129°C (free base)

^{1}H NMR (250MHz, $CDCl_3$) (free base)

δ: 8.22 (dd, J=8 and 1Hz, 1H), 7.80 (s, 1H), 7.20-7.42 (m, 8H), 3.90 (s, 3H), 3.88 (q, J=6Hz, 1H), 2.92-3.12 (m, 4H), 1.80 (s, 1H), 1.39 (d, J=6Hz, 3H).

5[2-(S)-(-)-α-Methylbenzylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E22)

mp 126-127°C

^{1}H NMR ($CDCl_3$) - as given for E21

5-[2-(Cyclohexylmethylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E23)

mp 204-205°C (HCl salt)

^{1}H NMR (250MHz, CD_3SOCD_3) (HCl salt)

δ: 9.23 (s, 2H), 8.13 (s, 1H), 8.03 (d, J=8Hz, 1H), 7.58 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 3.90 (s, 3H), 3.40-3.58 (m, 4H), 2.85 (d, J=6Hz, 2H), 1.60-1.90 (m, 6H), 0.90-1.33 (m, 3H), 0.89-1.08 (m, 2H).

5-[2-(3,3-Dimethylbutylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E24)

mp 215-217°C (HCl salt)

^{1}H NMR (250MHz, CD_3SOCD_3) (HCl salt)

δ: 9.33 (s, 2H), 8.13 (s, 1H), 8.04 (d, J=8Hz, 1H), 7.58 (d, J=8Hz, 1H), 7.20-7.38 (m, 2H), 3.89 (s, 3H), 3.48 (m, 4H), 3.00 (m, 2H), 1.58 (m, 2H), 0.90 (s, 9H).

5-[2-(1,3-Dimethylbutylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E25)

mp 182-183°C (HCl salt)

^{1}H NMR (250MHz CD_3SOCD_3) (HCl salt)

δ: 9.30 (s, 2H), 8.12 (s, 1H), 8.05 (d, J=6Hz, 1H), 7.60 (d, J=6Hz, 1H), 7.20-7.38 (m, 2H), 3.89 (s, 3H), 3.50 (m, 4H), 3.30 (m, 1H), 1.52-1.80 (m, 2H), 1.42 (m, 1H), 1.28 (d, J=6Hz, 3H), 0.93 (d, J=6Hz, 3H), 0.88 (d, J=6Hz, 3H).

5-[2-(N-Methyl-N-benzylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E26)

mp 156-158°C (HCl salt)

^{1}H NMR (250MHz, CD_3SOCD_3) (HCl salt)

δ: 11.4 (s, 1H), 8.13 (s, 1H), 8.03 (d, J=8Hz, 1H), 7.67 (m, 2H) 7.58 (d, J=8Hz, 1H), 7.48 (m, 3H), 7.20-7.38 (m, 2H), 4.52 (m, 1H), 4.37 (dd, J15 and 5Hz, 1H), 3.89 (s, 3H), 3.50-3.78 (m, 4H), 2.75 (d, J=5Hz, 3H).

5-[2-(Benzylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole (E27)

mp 207-207°C (HCl salt)

^{1}H NMR (250 MHz, CD_3SOCD_3) (HCl salt)

δ: 9.75 (s, 2H), 8.13 (s, 1H), 8.04 (d, J=8Hz, 1H), 7.56-7.68 (m, 3H), 7.42-7.52 (m, 3H), 7.20-7.38 (m, 2H), 4.26 (s, 2H), 3.40-3.55 (m, 4H).

***cis*-5-[2-(4-Methylcyclohexylamino)ethyl]-(1-methylindol-3-yl)-1,2,4-oxadiazole** (E28)

mp 214-216°C (HCl salt)

^{1}H NMR (400MHz, CD_3SOCD_3) (HCl salt)

δ: 9.27 br (s, 2H), 8.11 (s, 1H), 8.05 (d, J=8Hz, 1H), 7.57 (d, J=8Hz, 1H), 7.21-7.35 (m, 2H), 3.89 (s, 3H), 3.41-3.54 (m, 4H), 3.15-3.25 (m, 1H), 1.64-1.85 (m, 5H), 1.43-1.54 (m, 4H), 0.92 (d, J=6Hz, 3H).

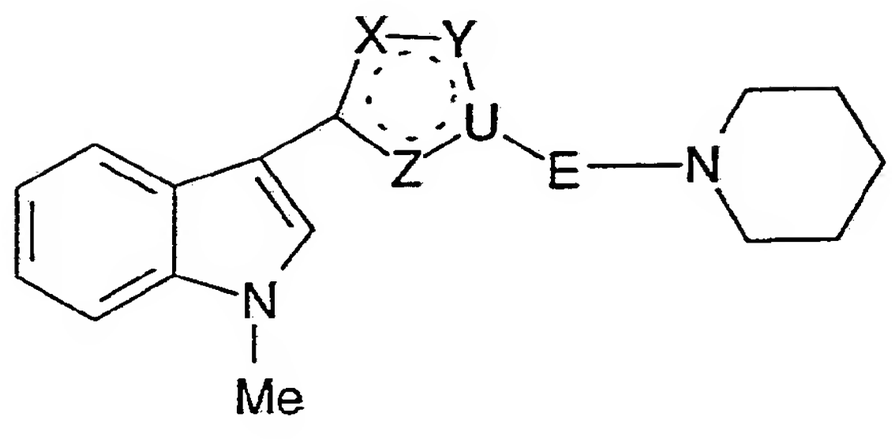
***trans*-5-[2-(4-Methylcyclohexylamino)ethyl]-3-(1-methylindol-3-yl)-1,2,4-oxadiazole** (E29)

mp 206-208°C (HCl salt)

^{1}H NMR (400MHz, CD_3SOCD_3) (HCl salt)

δ: 9.23 br (s, 2H), 8.12 (s, 1H), 8.04 (d, J=8Hz, 1H), 7.58 (d, J=8Hz, 1H), 7.22-7.38 (m, 3H), 3.89 (s, 3H), 3.32 (s, 4H), 2.99-3.10 (m, 1H), 2.10 (m, 2H), 1.74 (m, 1H), 1.25-1.50 (m, 3H), 0.90-1.02 (m, 4H), 0.87 (d, J=6Hz, 3H).

Examples 30 to 36



Example	X	Y	Z	U	E
E30	N	N	N	N	$(CH_2)_2$
E31	N	S	N	C	S-$(CH_2)_2$
E32	N	C	N	N	$(CH_2)_2$
E33	N	N	O	C	$(CH_2)_2$
E34	O	N	N	C	$(CH_2)_2$
E35	N	O	N	C	NH-$(CH_2)_2$
E36	C	S	N	C	$(CH_2)_2$

Example 30

3-(2-Piperidylethyl)-5-(l-methyl-1H-indol-3-yl)tetrazole (E30)

3-(l-Acetylpiperidyl)-5-(l-methyl-1H-indol-3-yl) tetrazole (0.080g, 0.247 mmol) (D3) was dissolved in dry THF (2 ml) and added to 1M borane-tetrahydrofuran complex (0.741 ml, 0.741 mmol). The mixture was heated to reflux under N_2. After 1h, a further amount of 1M borane-tetrahydrofuran complex (0.741 ml, 0.741 mmol) was added. The mixture was then heated under reflux for a further 0.5h, before being allowed to cool. 4M HCl in methanol (1 ml) was then added and the mixture then heated under reflux for 1h, allowed to cool, and evaporated under reduced pressure to give an oily solid which was treated with 10% NaOH. The aqueous mixture was then extracted with $CHCl_3$(2x). The combined organic layers were dried (Na_2SO_4) and evaporated to give the title compound as a colourless oil (0.065g, 85%), which crystallised on standing, and was converted to its hydrochloride salt.

mp (HCl salt) 228-230°C

^{1}H NMR (250 MHz, CD_3SOCD_3) (HCl salt)

δ: 11.15 (1H,s).60(1H, d, J=8Hz), 7.30(2H,m), 5.32(2H, t, J=5Hz), 3.90(3H, s), 3.80(2H,m), 3.50(2H,m), 3.00(2H,m), 1.90-1.60(5H,m), 1.50-1.30(1H,m)

Example 31

5(1-Thio-2-(piperidino)ethyl)-3-[1-methyl-1-H-indol-3-yl]-1,2,4-thiadiazole (E31)

5-Thio-3-[1-methyl-1H-indol-3-yl]-1,2,4-thiadiazole (0.112g, 0.453 mmol) (D4) was dissolved in ethanol (4ml) and sodium hydride (80%) (0.014g, 0.475 mmol) was added with stirring:1-(2-Chloroethyl)piperidine hydrochloride was then dissolved in ethanol (2 ml) containing sodium hydride (80%) (0.014g, 0.475 mmol). The resultant solution was then added to the solution of the thiol. The mixture was then heated under reflux, under N_2. After 4h, the reaction mixture was allowed to cool and

was evaporated under reduced pressure to give an orange solid, which was partitioned between $CHCl_3$ and water. The aqueous layer was then extracted with $CHCl_3$ and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil (0.130g). The oil was then purified by silica-gel chromatography (2:1 pentane EtOAc as eluant) to give the title compound as a colourless oil (0.110g, 68%), which was converted to its hydrochloride salt.

mp (HCl salt) 197-200°C

^1H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.45(1H,m), 7.90(1H,s), 7.40-7.20(3H,m), 3.89(3H,s), 3.50(2H, t, J=6Hz), 2.82(2H, t, J=6Hz), 2.54(4H,m), 1.65(4H,m), 1.47(2H,m)

Example 32

1-[2-Piperidylethyl]-3(1-methyl-1H-indol-3-yl)-1,2,4-triazole hydrochloride (E32)

1-[1-Acetylpiperidyl]-3-(1-methyl-1H-indol-3-yl)1,2,4-triazole (0.080g, 0.248 mmol) (D5) was dissolved in dry THF (3 ml) and added to 1M borane-tetrahydrofuran complex (1.24 ml, 1.24 mmol). The mixture was then heated to reflux under N_2 with stirring. After 2.5h the mixture was allowed to cool and 4M HCl in methanol was added. The reaction was then heated to reflux for 1h before being allowed to cool, and was then evaporated under reduced pressure. The residue was then partitioned between $CHCl_3$ and 10% sodium hydroxide solution. The aqueous layer was then extracted with $CHCl_3$ and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a colourless oil, which was purified by silica-gel chromatography (EtOAc:MeOH 20:1) to give the title compound as a colourless oil (0.025g 33%), which was converted to its hydrochloride salt.

mp. 195-197°C

^1H NMR (250 MHz, $CDCl_3$) (free base)

δ: 8.34(1H, d, J=8Hz), 8.18(1H,s), 7.73(1H,s), 7.38-7.20(3H,m), 7.38-7.20(3H,m), 4.28(2H, t, J=6Hz), 3.85(3H,s), 2.82(2H, t, J=6Hz), 2.45(4H,m), 1.56-1.38(6H,m)

Example 33

5-[2-(Piperidyl)ethyl]-3-(1-methyl-1H-indol-3-yl)-1,3,4-oxadiazole (E33)

1-[3-(1-Piperidyl)propionyl]-2-[3-carbonyl-1-methyl-1H-indol-3-yl]-hydrazide (0.280g, 0.854 mmol) (D6) was dissolved in $POCl_3$ (4 ml) and heated to reflux with stirring. After 0.75 h, the reaction mixture was allowed to cool and was poured carefully into water (15 ml). Solid sodium bicarbonate was then added to the mixture until pH 8 was reached. The resultant yellow sludge was then extracted with CH_2Cl_2 (3x). The combined organic layers were then dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil, which was purified by silica-gel chromatography (EtOAc:MeOH 10:1 as eluant) to give the title compound as a colourless oil (0.148g, 56%), which was converted to its hydrochloride salt.

mp (HCl salt) 222-223°C

^1H NMR (250 MHz, CD_3SOCD_3) (HCl salt)

δ: 10.82(1H,s), 8.20(1H,s), 8.10(1H, d, J=8Hz), 7.60(1H, d, J=8Hz), 7.30(2H,m), 3.92(3H,s), 3.55(6H,m), 3.10-2.90(2H,m), 1.90-1.65(5H,m), 1.50-1.30(1H,m)

Example 34

3-[2-Piperidylethyl]-5-[1-methyl-1H-indol-3-yl]-1,2,4-oxadiazole (E34)

3-(1-Piperidyl)propionamide oxime (0.903 g, 5.28 mmol) (D7) was dissolved in dry THF (40 ml) containing ground 4A molecular sieves (3.0g). After 0.5 h sodium hydride (0.346 g, 5.76 mmol) was added and the mixture was heated to reflux under N_2. Meanwhile (1-methyl-1H-indol-3-yl carboxylic acid) (J. Org. Chem. 1958 23, 1096) (0.840g, 4.80 mmol) was suspended in (CH_2Cl_2(30 ml) and oxalyl chloride was added (0.628g, 7.20 mmol), followed by a drop of dry DMF. The mixture was then stirred at room temp. for 1.5h, before being evaporated under reduced pressure and dried *in vacuo* to give the crude acid chloride, which was then dissolved in dry THF (10 ml) and added to the refluxing solution of the amidoxime salt (after 1.5h). After 3h the reaction mixture was allowed to cool, was filtered and the filtrate evaporated under reduced pressure to give a brown oil, which was purified by silica-gel chromatography (2% MeOH in $CHCl_3$ as eluant) to give the title compound as a colourless oil (0.546 g, 37%) which was converted to its hydrochloride salt.

mp (HCl salt) 174-176°C

^1H NMR (250 MHz, CD_3SOCD_3) (HCl salt)

δ: 11.00(1H,s), 8.40(1H,s), 8.12(1H,d, J=8Hz), 7.63(1H, d, J=8Hz), 7.40-7.20(2H,m), 3.92(3H,s), 3.60-3.35(6H,m), 3.00(2H,m), 1.95-1.55(5H,m), 1.40(1H,m)

Example 35

5[1-Amino-2-(piperidyl)ethyl]-3-[1-methyl-1H-indol-3-yl]-1,2,4-oxadiazole (E35)

5-Trichloromethyl-3-[1-methyl-1H-indol-3-yl]-1,2,4-oxadiazole (0.100g, 0.316 mmol) (D8) was dissolved with stirring in 1-(2-aminoethyl) piperidine (0.8 ml) and heated to 120°C. After 0.5h, the reaction mixture

was allowed to cool and was partitioned between EtOAc and water. The organic layer was then washed with water (1x), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil which was purified by silica gel chromatography (10% MeOH in EtOAc as eluant) to give the title compound as a colourless oil that crystallised on standing (0.095g, 93%).

mp 146-147°C from CH_2Cl_2/petrol

^1H NMR (250 MHz, $CDCl_3$)
δ: 8.20(1H,dd, J=8 and 1Hz), 7.70(1H,s), 7.40-7.20(3H,m), 6.10(1H,s), 3.89(3H,s), 3.54(2H,q, J=6Hz), 2.60(2H, t, J=6Hz), 2.45(4H,s), 1.60(4H,m), 1.48(2H,m)

Example 36

5-[1H-Indol-3-yl]-2-[2-piperidylethyl]-1,3-thiazole (E36)

The title compound was prepared from 3-bromoacetylindole and 1-(3-amino-3-thioxopropyl)piperidine according to the method of Rosen T., Nagel A.A. *et al,* J. Med. Chem 1990, **33**, 2715-2720.

mp 155-7°C

^1H NMR (250MHz, CD_3SOCD_3 (HCl salt)
δ: 11.4 (1H,s), 8.07(1H,d), 7.87(1H,d), 7.70(1H,s), 7.43(1H,d), 7.14(2H,m), 3.55(6H,m), 2.9-3.2(2H,m), 1.7-1.95(5H,m), 1.3-1.5(1H,m)

Descriptions

Description 1 (intermediate for Example 14)

2-Methoxy-4-amino-5 chlorobenzamide - Oxime

Sodium (0.245g, 10.62 mmol) was dissolved in methanol (10 ml). Hydroxylamine hydrochloride (0.738g, 10.62 mmol) in methanol (10 ml) was then added to the stirred solution. The mixture was then stirred at room temperature for ½h, before being filtered. The filter pad was then washed with methanol (~10 ml) and the filtrate was treated with 2-methoxy-4-amino-5-chlorobenzonitrile (A. Morimoto and Y. Saito, Jap. patent 71 03, 368, C.Abs 74, 111779h). The mixture was then heated to reflux with stirring. After 24h, the reaction mixture was allowed to cool, and was then evaporated under reduced pressure to give a yellow solid. The solid was then recrystallised from methanol. The resulting pale yellow solid was then dried *in vacuo* to give the title compound (D1) (0.462g, 40%). m.pt. 178-181°C.

^{1}H NMR (250 MHz, (CD_3SOCD_3)

δ: 9.28 (s, 1H), 7.20 (s, 1H), 6.48 (s, 1H), 5.58 (s, 2H), 5.48 (s, 2H), 3.70 (s, 3H).

Description 2 (intermediate for Example 15)

5-Ethenyl-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadiazole

1-Methyl-1H-indole-3 carboxamide oxime (C J Swain *et al*, J Med Chem, 1991, **34**, 147) (0.500 g, 2.64 mmol) was dissolved in dry THF (20 ml) with stirring, and treated with ground 4A molecular sieves (1.5 g) under nitrogen. After 30 minutes sodium hydride (80% dispersion in mineral oil) (0.087 g, 2.91 mmol) was added. The mixture was then heated to reflux. After 30 minutes the mixture was allowed to cool momentarily and a methyl acrylate (0.475 ml, 5.28 mmol) was added. The mixture was

then heated to reflux for a further 3 hours. The reaction mixture was then allowed to cool and was filtered. The filter pad was then washed with THF (2X). The filtrate was then evaporated under reduced pressure. The residue was purified by silica-gel chromatography eluting with pentane EtOAc 3:1 to afford the title compound (D2) as a colourless oil that crystallised on standing mpt 53-55°C.

^{1}H NMR (250 MHz, $CDCl_3$)

δ: 8.25 (m; 1H), 7.80 (s, 1H), 7.26-7.42 (m, 3H), 6.70-6.85 (dd, J=18, 11 Hz), 6.56 (d, J=18Hz, 1H), 5.98 (d, J=11Hz, 1H), 3.79 (s, 3H).

Description 3 (intermediate for Example 30)

a) 5-(l-Methyl-1H-indol-3-yl)tetrazole

3-Cyano(l-methyl-lH-indole) (J. Med. Chem. 199, 34, 147) (0.500g, 3.21 mmol) was dissolved in dry DMF (4 ml) and treated with ammonium chloride (0.214g, 4.01 mmol) and sodium azide (0.260g, 4.01 mmol). The mixture was then heated to reflux with stirring. After 26h, the reaction mixture was allowed to cool and was evaporated under reduced pressure to give a brown oil. Water (15 ml) was added to this residue whereupon it solidified. The mixture was made strongly basic with sodium hydroxide solution and then extracted with diethyl ether. The aqueous layer was then treated with activated charcoal and heated on a water bath for 10 minutes. The mixture was then filtered and the filtrate acidified with 5M HCl to pH4. The resulting brown precipitate was then filtered off and dried *in vacuo* to give the title compound (0.125g, 20%) as a pale brown solid.

^{1}H NMR (250 MHz, CD_3SOCD_3)

δ: 8.24(1H,dd, J=7 and 1Hz), 8.08(1H, s), 7.60(1H, dd, J=7 and 1Hz), 7.30(2H, m) 3.91(3H,s).

b) 3-(l-Acetylpiperidyl)-5(l-methyl-IH-indol-3-yl)tetrazole

5-(l-Methyl-1H-indol-3-yl)tetrazole (0.080g, 0.402mmol) was dissolved in dry THF (5 ml) and treated with sodium hydride (80%) (0.014 g, 0.441 mmol). When effervescence had ceased, l-(bromoacetyl)piperidine (Bull. Soc. Chim. France 1964 5, 1063) (0.093g, 0.422 mmol) in dry THF (2 ml) was added. After 1h, a further amound of l-(bromoacetyl)piperidine (0.047g, 0.211 mmol) in dry THF (1 ml) was added. After a further 2h, the reaction mixture was evaporated under reduced pressure to give a brown solid which was partitioned between $CHCl_3$ and water. The organic layer was washed with $NaHCO_3$ solution, and the combined aqueous layers were extracted with $CHCl_3$. The combined organic layers were then dried (Na_2SO_4) and evaporated to give an off white foam which was dried *in vacuo* and then purified by silica-gel chromatography (pentane: EtOAc 1:1 as eluant) to give the title compound (D3) as a white solid (0.080 g, 61%)

1H NMR (250 MHz, $CDCl_3$)

δ: 8.32(1H, dd, J=7 and 1Hz), 7.88(1H,s), 7.32(3H, m), 5.53(2H,s), 3.89(3H,s), 3.60(2H,t, J=5Hz), 3.48(2H, t, J=5Hz), 1.62(6H, m)

Description 4 (intermediate for Example 31)

5-Thio-3-[l-methyl(-1H-indol-3-yl]-1,2,4-thiadiazole

3-[l-Methyl(-1H-indol-3-yl]carboxamide oxime (J. Med. Chem. 199, 34, 147) was dissolved in dry THF (10 ml). Ground 4A molecular sieves (1.0g) were then added and the mixture was stirred at room temp. Sodium hydride (80%) (0.052g, 1.746 mmol) was then added and the mixture heated to reflux for 0.5h. Carbon disulphide (0.286 ml, 4.76 mmol) was then added. Reflux was maintained for a further 2h, before the reaction mixture was allowed to cool. The reaction mixture was then filtered and the filtrate evaporated under reduced pressure. The resultant brown oil was then purified by silica-gel chromatography (1:1 Pentane:EtOAc as eluant) to give the title compound as a yellow solid (0.080g, 20%) (D4)

^1H NMR (250 MHz, CD_3SOCD_3)

δ: 8.30(1H, s), 8.20(1H,d, J=7Hz), 7.58(1H, d, J=7Hz), 7.28(2H,m), 3.89(3H,s).

Description 5 (intermediate for Example 32)

a) 3-(1-Methyl-1H-indol-3-yl)1,2,4-triazole

Methyl(1-methyl-1H-indol-3-yl)imidate hydrochloride (J. Chem. Soc. Perkin. Trans. 1, 1990, 3183) was dissolved with stirring in dry methanol (10 ml) and treated with triethylamine (0.123 ml, 1.069 mmol). The reaction mixture was then stirred at room temperature for 0.25 h, then formyl hydrazide (0.064g, 1.069 mmol) was added. The mixture was heated to reflux and after 7h the reaction mixture was allowed to cool and was evaporated under reduced pressure. The solid residue was then dissolved in formic acid (10 ml) and refluxed for 0.75 h. The reaction mixture was allowed to cool and then evaporated under reduced pressure and purified by silica-gel chromatography (EtOAc as eluant) to give the title compound as a colourless oil (0.055g, 31%).

^{1}H NMR (250 MHz, $CDCl_3$)

δ: 8.20 (1H, d, J=8Hz), 8.15(1H,.s), 7.60(1H,s), 7.32-7.15(3H,m), 3.65(3H,s)

b) 1-[1-Acetylpiperidyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-triazole

3-(1-Methyl-1H-indol-3-yl)-1,2,4- triazole (0.190g, 0.960 mmol) was dissolved with stirring in dry THF (5 ml) and was treated with sodium hydride (80%) (0.032g, 1.05 mmol), followed by 1-(bromoacetyl)piperidine (Bull. Soc, Chim. Fr. 1964, 5, 1063-9) (0.232g, 1.05 mmol) in dry THF (1 ml). After 4h, the reaction mixture was evaporated under reduced pressure and partitioned between EtOAc and water. The organic layer was then dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil, which was purified by silica-gel chromatography (EtOAc -> EtOAc:MeOH 100:1 as eluant) to give the title compound (D5b) as a white solid (0.080g, 26%).

^1H NMR (250 MHz, $CDCl_3$)

δ: 8.32(1H, dd, J=7 and 1Hz), 8.21(1H,s), 7.40-7.20(3H,m), 5.06(2H, s) 3.85(3H, s), 3.62-3.48(4H,m), 1.72-1.50(6H,m).

Description 6 (intermediate for Example 33)

1-[3-(1-Piperidyl)propionyl]-2-[3-carbonyl-1-methyl(-1H-indol-3-yl]hydrazide

1-Methyl-1H-indole-3-carboxylic acid (J. Org. Chem 1958 23 1096-1097), (0.614g, 3.51 mmol) was suspended in dry CH_2Cl_2 (15 ml) and treated with oxalyl chloride (0.459 ml, 5.26 mmol) with stirring, followed by a drop of DMF. After 0.75h, the reaction mixture was evaporated under reduced pressure and dried *in vacuo*. The orange solid produced was then redissolved in CH_2Cl_2 (15 ml), triethylamine (0.512 ml, 3.86 mmol) was then added, followed by [3(1-piperidyl)propionyl]hydrazide (Seances Acad. Sci. Ser. C. (1976) 282 (17) 857-60) (0.600g, 3.51 mmol) in CH_2Cl_2 (4 ml). The mixture was stirred at room temperature overnight, and washed with sodium bicarbonate solution (2X). The organic layer was dried (Na_2SO_4) and evaporated to give a cream solid, which was purified by silica gel chromatography (20% EtOH in $CHCl_3$ as eluant) to give the title compound (D6) (0.280g, 24%) as a white solid.

^1H NMR (250 MHz, $CDCl_3$)

δ: 9.22(1H,s), 8.10(1H,m), 7.72(1H,s), 7.30-7.10(3H,m), 3.60(3H,s), 2.70(3H,m), 2.55(4H,m), 1.75(4H,m), 1.60-1.40(2H,m)

Description 7 (intermediate for Example 34)

3(1-Piperidyl)propionamide oxime

Sodium (1.09g, 0.047 mol) was added carefully to methanol (10 ml) under N_2 with stirring. When all the sodium had dissolved, a solution of

hydroxylamine hydrochloride (3.29g, 0.047 mol) in methanol (30 ml) was added slowly. The mixture was then stirred at room temp for 1/2 h before being filtered. The filtrate was then treated with 3(1-piperidyl)propionitrile (Chem. Abs. 47, 9906) (3.27g, 0.024 mol) and the mixture heated to reflux. After 7.5h the reaction mixture was allowed to cool and was then evaporated under reduced pressure. The residue was then triturated with diethylether to give a white solid which was filtered off and dried *in vacuo* the title compound (3.30g, 82%) (D7)

^{1}H NMR (250 MHz, CD_3SOCD_3)

δ: 9.0(1H,s), 5.60(2H,s), 3.05-2.85(6H,m), 2.42(2H, t, J=6Hz), 1.70(4H,m), 1.50(2H,m)

Description 8 (intermediate for Example 35)

5-Trichloromethyl-3-[1-methyl-1H-indol-3-yl]-1,2,4-oxadiazole

1-Methyl-1H-indole-3-carboxamide oxime (J. Med. Chem. 1991 34, 147) (2.00g, 0.011 mol) was added to trichloroacetic anydride (20 ml) with ice cooling and stirring. The mixture was then stirred at room temperature. After 2.5h, the reaction mixture was poured onto a mixture of ethyl acetate and aqueous sodium bicarbonate. The aqueous layer was then extracted with ethyl acetate and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow solid which was purified by silica-gel chromatography (Pentane: EtOAc 10:1) to give the title compound as a cream coloured solid (1.29g, 39%).

^{1}H NMR (400 MHz,$CDCl_3$)

δ: 8.20(1H,dd, J=8 and 1Hz), 7.88(1H,s), 7.40-7.20(3H,m), 3.89(3H,s)

5-HT_4 RECEPTOR ANTAGONIST ACTIVITY

1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}M and granisetron 10^{-6}M to block effects at 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum(10^{-9}M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT_4 receptor antagonist are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP. From this data, pIC_{50} values are determined, being defined as the -log concentration of antagonist which reduces the contraction by 50%. A compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor antagonist.

The compound of Example 21 of EP-A-328200 had a pIC_{50} of 7.3.

Compounds were generally active in the range of concentrations of the order of pIC_{50}=6 or more, E1 and E3 showing particularly good activity.

2) Piglet Atria

Compounds were tested in the piglet spontaneous beating screen (Naunyn-Schmiedeberg's Arch. Pharmacol 342, 619-622). pK_B

($-\log_{10} K_B$) value for the compound of Example 21 of EP-A-328200 was 7.6.

3) Rat oesophagus

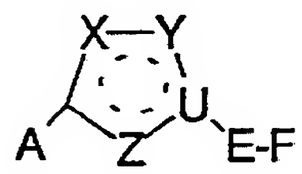
Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100μM for 15 min followed by washout) and in the presence of cocaine (30μM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3μM).

4) 5-HT-induced motility in dog gastric pouch

Compounds are tested for inhibition in the *in vivo* method described in "Stimulation of canine motility by BRL 24924, a new gastric prokinetic agent", Bermudez *et al*, J. Gastrointestinal Motility, 2(4), 281-286.

Claims

1. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof;



(I)

wherein A, X, Y, Z, U, E and F are as defined in the specification, in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

2. The use according to claim 1 for use as a 5-HT_4 antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

3. The use according to claim 2 for use in the treatment of IBS.

4. The use according to claim 2 for use in the treatment of gastro-oesophagal reflux disease and dyspepsia.

5. The use according to claim 2 for use in the treatment of atrial arrhythmias and stroke.

6. The use according to claim 2 for use in the treatment of anxiety.

7. The use according to claim 2 for use in the treatment of migraine.

8. The use of 1-methyl-1,3-[5-(2-(1-piperidyl)ethyl)-1,2,4-oxadiazol-3-yl]indole or any one of the compounds of the Examples, E1 to E36, in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

9. A compound selected from the compounds of Examples 1 to 36, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound according to claim 9, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/01419

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/41 A 61 K 31/445 A 61 K 31/435
A 61 K 31/54 A 61 K 31/55 C 07 D 413/04 C 07 D 413/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K 31/00

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0328200 (MERCK SHARP & DOHME) 16 August 1989, see page 3, paragraph 1; page 11, lines 26-55; claim 9 (cited in the application)	8
Y	Journal of Medicinal Chemistry, vol. 34, no. 1, January 1991, American Chemical Society, C.J. SWAIN et al.: "Novel 5-HT3 antagonists. Indole oxadiazoles", pages 140-151, see the entire document (cited in the application)	8
Y	J. Auton. Pharmacol., vol. 5, no. 2, June 1985, P.R. SAXENA et al.: "Excitatory 5-hydroxytryptamine receptors in the cat urinary bladder are of the M-and 5-HT2-type", pages 101-107, see the entire document	8

-/-

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02-11-1992	30. 12. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,0189002 (SANDOZ) 30 July 1986, see page 19 (cited in the application) ---	8
Y	EP,A,0200444 (BEECHAM) 5 November 1986, see page 20, last paragraph - page 21, line 16 (cited in the application) ---	8
Y	European Journal of Pharmacology, vol. 183, no. 4, July 1990, Elsevier Science Publishers B.V., M.A. PETTY et al.: "Anti arrhythmic activity of the 5-HT3 receptor antagonist MDL 73147 in different species", page 1159, see the entire document ---	8
Y	Naunyn-Schmiedeberg's Arch. Pharmacol., vol. 342, no. 5, November 1990, A.J. KAUMANN: "Piglet sinoatrial 5-HT receptors resemble human atrial 5-HT4-like receptors", pages 619-622, see the entire document (cited in the application) -----	8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB92/01419

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
THE SUBJECT MATTER OF CLAIMS 1-10 VIOLATES THE REQUIREMENTS OF ART.6 AND RULE 6.2 PCT. ONLY CLAIM 8 WAS FOUND TO BE PARTIALLY SEARCHABLE. THE ATTENT ION OF THE APPLICANT IS DRAWN TO THE FACT THAT UPON FILING OF AMENDED CLAI MS, UNITY OF INVENTION HAS TO BE REASSESSED, AND THIS COULD RESULT IN A POSSIBLE REQUEST FOR PAYMENT OF ADDITIONAL SEARCH FEES.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201419 SA 62913

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 08/12/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0328200	16-08-89	AU-A- 2986089	17-08-89
		JP-A- 1268687	26-10-89
		US-A- 4952587	28-08-90
		US-A- 5041456	20-08-91
EP-A- 0189002	30-07-86	DE-A- 3446484	03-07-86
		DE-A- 3531281	12-03-87
		DE-A- 3531282	12-03-87
		AU-B- 595172	29-03-90
		AU-A- 5139685	31-07-86
		JP-A- 2237920	20-09-90
		JP-A- 61152628	11-07-86
EP-A- 0200444	05-11-86	AU-B- 594670	15-03-90
		AU-A- 5657986	06-11-86
		CA-A- 1296004	18-02-92
		EP-A- 0498466	12-08-92
		JP-A- 61275276	05-12-86
		US-A- 4937247	26-06-90
		US-A- 4886808	12-12-89
		US-A- 5034398	23-07-91
		EP-A- 0223385	27-05-87